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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/706,580	Applicant(s) CUNNINGHAM, JANET	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 26-37* is/are pending in the application.

4a) Of the above claim(s) *1-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24 and 26-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Please note that the Examiner of record has changed in the instant application. Please direct future correspondence to Examiner Schmidt (see the concluding remarks below for information on how to reach the Examiner).

2. Applicant's election without traverse of Group V, in Paper No. 9 is acknowledged. The pending claims encompassed by the elected Group V are now claims 24 and 26-37.

Claims 1-23 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 9, filed 10/18/01.

3. The instant Official Action is non-final in view of the new rejection.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 24 and 26-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stratagene's Complete Control System for Inducible Mammalian Expression published in the

Stratagene newsletter, Vol. 12, No. 1, first quarter, 1999, under the title of "Versatile Vectors for Ponasterone A- Inducible Control of Gene Expression in Mammalian Cells" by Denise Wyborski and Peter Vaillancourt (publication on http://www.stratagene.com/vol12_1/p1-4.htm) in view of Natesan et al. (U.S. Patent 6,117,680) and Natesan (U.S. Patent6,015,709).

Claims 24, 30 and 31 are drawn to methods for inducing gene expression in a mammalian cell via (1) transducing the mammalian cell with two AAV virion having different vectors-- one AAV vector comprising a transcriptional promoter region comprising at least one ecdysone-responsive element (EcRE), and a promoter capable of directing the *in vivo* transcription of said polynucleotide of interest in a mammalian cell, located downstream of the at least one EcRE; and the second AAV vector that comprises a coding sequence encoding an ecdysone receptor (EcR) and further comprises a coding sequence encoding a retinoid-X-receptor (RXR), wherein said EcR and RXR coding sequences are operably linked to control elements capable of directing the in vivo transcription thereof in the mammalian cell; and (2) providing ecdysone, or an analog thereof capable of binding the EcR to said mammalian cell to induce the expression of the polynucleotide of interest; wherein the transcriptional promoter region comprises at least one enhancer, such as SP1.

Claims 26-29 and 32-34 are analogous to claims 24, 30 and 31, except, the mammalian cell is transduced with three vectors instead of two since the ecdysone receptor (EcR) and the retinoid-X-receptor (RXR) are encoded on different vectors.

Claims 35-37 are analogous to the above claims expect the transduced mammalian cell already comprises an RXR receptor and as such, the two vectors that are transformed into the cell are: (1) the first AAV vector comprising the transcriptional promoter region operably liked to a polynucleotide of interest, wherein the transcriptional promoter region comprises at least one ecdysone-responsive element (EcRE), and a promoter downsteam of the at least one EcRE; and (2) the second AAV vector comprising a coding sequence encoding an ecdysone receptor (EcR) operably linked to control elements.

Stratagene's complete control system discloses the use of two vectors for inducing gene expression in a mammalian cells having all the claimed limitations of claims 24, 30 and 31, except that the vectors taught by Stratagene are not AAV viral vectors as instantly claimed for AAV virion transduction of mammalian cells. Furthermore, they do not specifically teach the system having three vectors as claimed in instant claims 26-29 and 32-34 nor in cells already having the RXR receptor as in claims 35-37.

Natesan et al. (U.S. Patent 6,117,680) and Natesan (U.S. Patent 6,015,709) provided motivation and guidance for using AAV vectors and virion for transduction of mammalian cells (see especially '680, col. 39-42) including vectors using the ecdysone receptor system instantly claimed (see '680, col. 25, first para. or '709, col. 27, last full para.). They did not specifically teach vectors having all the claimed limitations.

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to transform mammalian cells with AAV viral vectors (taught by

Natesan) having the pertinent portions of the Stratagene vectors for ecdysone induced gene expression (those taught in Stratagene vectors pERV3 (the RXR receptor and the EcR receptor) and pEGSH (the 5xE/GRE and 3x SP1 enhancer sequences upstream of a heat shock promoter (HSP) and a multicloning site for introduction of the gene of interest). Stratagene et al. taught all the claimed features of gene expression and Natesan taught the guidance for design of AAV vectors expressing genes using the ecdysone inducible system.

One of ordinary skill in the art would have been motivated to induce gene expression from a vector that is regulated by ecdysone since Stratagene taught that "the complete control mammalian expression system allows tight control of gene expression in a wide range of mammalian cell types" since the "inducible promoter used in the system is naturally repressed in the absence of the ecdysone analog ponasterone A (ponA)." Natesan provided the motivation to use this system coupled with AAV viral vectors for cell transduction.

Both Stratagene and the Natesan et al. provided explanations of the ecdysone receptor system instantly claimed applicable to cells transduced by two or three vectors so long as all the necessary components were present on the vectors (see pages 1-2 of Stratagene). For instance, the mammalian retinoid-X-receptor (RXR) for heterdimerizing to the *Drosophila* ecdysone receptor (EcR), may be supplied on a vector to the mammalian cell either on the same vector or different vectors, or the cell may be transduced to express the RXR prior to introducing the EcR vector. Natesan et al. provided a further expectation of success that AAV viral vectors may be used with this system for expression of a desired gene in the mammalian cell. He provided all the

important considerations for design and use of AAV vectors. Since vector construction is a piecemeal practice, one of ordinary skill in the art would have had an expectation of success for design of AAV vectors having the elements of the ecdysone inducible system for gene expression in mammalian cells based on the disclosure of all the necessary components in the Stratagene system, and of the AAV vectors components by Natesan.

Response to Arguments

Applicant's response to any potential 35 U.S.C. 103 rejections on pages 10-11 is addressed here.

Applicant summarizes that three basic criteria must be met to establish a prima facie case of obviousness according to MPEP 2143: (1) a suggestion/motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, (3) the combination of references must teach all the claimed limitations.

Since the instant rejection is no longer based on the teachings of Evans et al. and Srivastava, these criteria will be addressed in view of the above new combination of references: Stratagene and Natesan.

First, there was a suggestion/motivation to combine the reference teachings since Natesan taught use of AAV vectors/virion for transduction of cells, including use of the ecdysone induction system taught in substantial detail by Stratagene. The subject matter was the same, optimized transduction of cells for improved gene expression control, both making reference to

the ecdysone induction as the mechanism. Second, there was a reasonable expectation of success to specifically make AAV vectors having the necessary components of the ecdysone system taught by Stratagene since vector construction is well-known in the art and Natesan provided guidance on design of AAV vectors. Third, the combination of references taught all the claimed limitations since the use of different vectors for transducing the mammalian cell was taught by Stratagene and all the components of both AAV vectors and the ecdysone system (detailed above) were taught by both Stratagene and Natesan.

In view of the newly cited references, one of ordinary skill in the art would have reasonably expected that transducing a mammalian cell with multiple different AAV vectors would provide a fully functioning inducible gene expression.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

M. M. Schmidt
July 1, 2002

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SUPERVISORY PATENT EXAMINER
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